REMARKS

Claims 46, 54-77, and 80-107 are pending in the present application. Claims 46 and 74-76 have been amended to indicate that the surfactant and medicament are "suspended in the propellant as a finely divided powder." Claims 74 and 75 have been amended to specify that the added propellant is an HFA propellant. Claim 76 has been further amended to recite "a medicament for inhalation." Support for these amendments can be found throughout the specification and claims as filed, including at page 1, lines 12-13, and page 5, lines 5-12, *inter alia*.

35 U.S.C. § 112, second paragraph

Claims 46, 54-77 and 80-107 were rejected for allegedly failing to set forth the subject matter that Applicants regard as their invention. According to the Office action at page 2,

> Evidence that the claims fail to correspond in scope with that which applicant(s) regard as the invention can be found in Paper No. 34 filed (9/23/2003) (*sic*, 9/12/2003). In that paper, applicant has stated the formulations are non-aqueous, and this statement indicates that the invention is different from what is defined in the claims(s) because the claims do not exclude the presence of water.

Applicants traverse. While applicants did use the term "non-aqueous formulation" to describe the presently claimed formulations, that was meant as a general characterization based on the presence of hydrofluoroalkane (HFA) propellant in the formulations. Liquified HFAs are organic solvents that have relatively low miscibility in water. Thus, the term "non-aqueous formulation" as used in the response filed September 12, 2003, was meant to express the concept that the claimed formulations are based upon a non-aqueous organic liquid, as opposed to being based on water. While one would not expect to find an appreciable amount of water in an HFA-based formulation, and so the claimed formulations are easily distinguished from Meezan's water-based formulations, Applicants' use of the term "non-aqueous formulation" was not meant to imply that there could be no trace of water present. Thus, it would be inappropriate to add a limitation explicitly excluding the presence of water.

Furthermore, the claims implicitly exclude the presence of any substantial amount of water. The claims, as amended, require that the medicament and the alkyl saccharide are suspended in the propellant as a finely divided powder. As illustrated by Meezan's eyedrop examples, alkyl saccharides are soluble in water. In order for the claimed formulations to contain alkyl saccharide in powder form, there plainly must be little if any water present -- else the powder would dissolve in the water and no longer be a powder, taking the formulation outside of the claim. Thus, the claims as presently written clearly exclude fundamentally aqueous formulations such as those disclosed by Meezan.

Claims 76 and its dependent claims 77, 80-95, 106, and 107 were rejected for failing to recite "a medicament for inhalation" as required by the Examiner. Independent claim 76 has been amended to include the requested recitation.

For the foregoing reasons, Applicants request withdrawal of the rejections under 35 U.S.C. § 112, second paragraph.

35 U.S.C. § 103(a)

Claims 46, 54-77, and 80-107 were rejected as allegedly obvious over WO 91/11495 in view of Neale et al. (U.S. Pat. No. 5,688,782, "Neale"), Sequeira et al. (U.S. Pat. No. 5,837,699, "Sequeira"), and Meezan et al. (U.S. Pat. No. 5,661,130, "Meezan"). Applicants respectfully traverse.

Claims 46 and 76 require the presence of an HFA, a medicament for inhalation, and an alkyl saccharide surfactant. The alkyl saccharide surfactant is present to achieve a good dispersion of the particles of medicament in the HFA propellant, thereby achieving dose uniformity. As can be seen in Example 1 of U.S. Patent No. 6,524,557 (attached hereto as Exhibit A) issued to the present inventors, dodecylmaltoside, an alkyl saccharide, gives good suspensions in HFA propellant (Col. 5, lines 6-40, esp. line 35).

WO 91/11495 discloses nothing more than the general use of HFA propellants for medical aerosols including surfactants, with medicaments suspended in the propellant.

WO 91/11495 does not disclose or suggest the use of alkyl saccharide surfactants with HFA propellants.

Neale et al. discloses pharmaceutical beclomethasone ester monohydrate compositions comprising a fluorocarbon or hydrogen-containing chlorofluorocarbon propellant, and a vanishingly small amount of water. The Examiner argues that Neale teaches a "variety of other inhaled medicaments," *Office Action, page 4*, citing Col. 4, lines 29-68 and Col. 5, lines 1-5. Applicants fail to see the relevance of these teachings. Neale discloses that the addition of a minute amount of water (less than 0.1%) aids in the formation of stable beclomethasone aerosol formulations containing fluorocarbon or hydrogen-containing chlorofluorocarbon propellants. As Neale says, this is surprising, because

> The presence of water in conventional aerosol formulations is known to be associated with a number of potential problems and it is generally accepted that these preparations should be maintained **substantially free of water**.

See Col. 1, lines 55-58. (*emphasis added*) Neale does not disclose the use of an aqueous formulation – simply the surprising fact that the addition of a minute amount of water actually enhances the stability of beclomethasone formulations, which, as noted above, goes against the generally accepted idea that the presence of water in an aerosol including a fluorocarbon or hydrogen-containing chlorofluorocarbon propellant is not desirable. Nor is Neale suggesting the addition of water to any and all propellant-based aerosols. The "variety of other medicaments" referred to by the Examiner are disclosed as being possible additions to the beclomethasone formulations: "It will be appreciated by those skilled in the art that the aerosol formulations according to the invention may, if desired, contain one or more additional ingredients." (*emphasis added*)

Sequeira discloses formulations of mometasone furoate, which can be delivered as aerosolized particles suspended in a propellant (col. 5, lines 18-45) or as an aqueous suspension (col. 5, line 46-col. 6, line 7). Sequeira discloses the use of surfactants with aqueous suspensions of mometasone furoate (col. 5, line 63-col. 6, line 6), specifically reciting only Polysorbate 80 (col. 6 line 6), and the use of "the non-chlorofluorocarbons or alternate propellants such as the fluorocarbons, HFC-134A or HFC-227 with or without surfactants" (Col. 5 line 18-45). Nothing

in Sequeira explicitly or implicitly suggests the use of alkyl saccharide surfactants at all, let alone with a fluorocarbon propellant, or even suggests that surfactants that are suitable for use in an aqueous suspension might be suitable for use with a fluorocarbon propellant.

Meezan is directed to an aqueous formulation, wherein the active ingredient and surfactant are dissolved in water. This is in direct contrast with the formulation of the present invention, wherein the surfactant aids in dispersion of the medicament to form a suspension of finely divided particles in the liquefied propellant.

Meezan teaches the use of alkyl saccharides to increase bioavailability of an aqueous formulation *in vivo*; the alkyl saccharides and active ingredient are dissolved in the aqueous medium. In the claimed formulations, the alkyl saccharides remain in suspension as a finely divided powder, and do not dissolve in the propellant. The teachings of Meezan, while applicable to aqueous formulations, are irrelevant to the present formulations. While the term "aerosol" may be loosely used by some to refer to both an aqueous spray as described in Meezan and the powder particles suspended in hydrofluorocarbon-propellant gas as described in the present application, one of skill in the art would recognize that there is a world of difference between the two, both chemically and physically, and the skilled person seeking a solution to the problem of making good suspensions of powdered medicaments in hydrofluorocarbon propellants would thus not arrive at the claimed solution by applying the teaching of Meezan, which uses alkyl saccharides that dissolve in an aqueous solution for the stated purpose of increasing the absorption of a compound when it is administered with the compound via the ocular, nasal, nasolacrimal or inhalation route (see Col. 4, line 64 to Col. 5, line 3). In the present application, it is clear that the skilled person is dealing with a medicament in powder form, which is to be suspended, retaining its powder form, in a liquefied gas HFA propellant; there is no hint of a teaching or suggestion in Meezan as to what to add to such a mixture in order to get a good suspension.

The Examiner argues that "the mere fact that Meezan in its preferred examples discloses the use of an alkyl saccharide in aqueous solutions does not make the claimed invention unobvious." But the fact is that Meezan's only disclosure is of the use of alkyl saccharide in

aqueous solutions. Meezan never suggests the use of alkyl saccharides as surfactants in propellant-based aerosols, and one of skill in the art would not have been motivated to apply the teachings of Meezan, which solely describes formulations in which the surfactant and active ingredient are dissolved in an aqueous medium, to the claimed formulations, in which the medicament and surfactant are suspended as a finely divided powder in an HFA propellant.

The molecular hydrophilic or oleophilic strength of a surfactant is typically expressed as the hydrophile lipophile balance (HLB). As noted in the Preliminary Amendment submitted December 15, 2003, the HLB can predict whether a surfactant will form a water/oil colloid or an oil/water colloid. Few surfactants work equally well in both directions, their steric structure and the relative strengths of the polar or non-polar ends making them more suited to micelle formation in one orientation (i.e., hydrophobic in, hydrophilic out) than in the other orientation. Meezan et al. teach that alkyl saccharides are effective surfactants, i.e., they increase absorption, of medicaments delivered in an aqueous solution. Meezan suggests the use of surfactants with an HLB of 10 to 20, preferably 11 to 15, which are surfactants having stronger hydrophilic properties; this makes sense given the fact that the exemplary formulations disclosed in Meezan all comprise medicaments dissolved in an aqueous solution. The Examiner argues that the fact that surfactants can be formulated to have a lower HLB rescues the inapposite teachings of Meezan; Applicants respectfully disagree. Nowhere in Meezan is there any suggestion to alter the surfactants, which are disclosed therein as aids to dissolution of a compound in water, to render the surfactants useful as aids to dispersion of medicament to form a suspension in an HFA propellant.

The Examiner states that "it is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant, i.e., the same motivation. *In re Linter*..." (Office Action, page 5) Applicants do not disagree with this general principle. However, the fact remains that to establish a prima facie case of obviousness, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. MPEP §§2142 and 2143.01. Applicants submit that there was no motivation to

combine the references cited by the Examiner; the cited references completely fail to suggest the claimed combination at all, let alone for any other advantage or result. It is inarguable that nothing in WO 91/11495, Neale, Sequiera, or Meezan suggests the use of alkyl saccharides with fluorocarbon propellants, nor would anything in WO 91/11495, Neale, or Sequiera lead one of skill in the art to look to Meezan's disclosure of surfactants that dissolve in aqueous formulations to find a surfactant useful in the largely non-aqueous propellant-based formulations disclosed in WO 91/11495, Neale, and Sequiera. Thus, there is no teaching to combine the Meezan reference with the other references cited by the Examiner; Meezan is simply inapplicable, and, as there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify or combine reference teachings (discussed in MPEP § 2143.01), the Examiner's combination of four references rests on impermissible hindsight.

Thus, Applicants submit that the claimed invention is not obvious for at least the foregoing reasons, and request withdrawal of the rejection under 35 U.S.C. § 103(a).

Applicants submit that the claims as amended are allowable and request rapid notification of the same.

Enclosed is a check for the Petition for Extension of Time fee. Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

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